HHS Public Access
Author manuscript
J Occup Environ Med. Author manuscript; available in PMC 2015 September 14.

Published in final edited form as:
J Occup Environ Med. 2014 September ; 56(9): 901–910. doi:10.1097/JOM.0000000000000249.

Reproductive Health Risks Associated with Occupational Exposures to Antineoplastic Drugs in Health Care Settings: A Review of the Evidence

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Abstract

Objectives—Antineoplastic drugs are known reproductive and developmental toxicants. Our objective was to review the existing literature of reproductive health risks to workers who handle antineoplastic drugs.

Methods—A structured literature review of 18 peer-reviewed, English language publications of occupational exposure and reproductive outcomes was performed.

Results—While effect sizes varied with study size and population, occupational exposure to antineoplastic drugs appears to raise the risk of both congenital malformations and miscarriage. Studies of infertility and time-to-pregnancy also suggested an increased risk for sub-fertility.

Conclusions—Antineoplastic drugs are highly toxic in patients receiving treatment and adverse reproductive effects have been well documented in these patients. Healthcare workers with chronic, low level occupational exposure to these drugs also appear to have an increased risk of adverse reproductive outcomes. Additional precautions to prevent exposure should be considered.

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Keywords

antineoplastic drugs; healthcare; occupational exposures; pregnancy and adverse reproductive effects

Introduction

Healthcare workers who prepare or administer antineoplastic drugs, or who work in areas where these drugs are used can be exposed to these agents when they are present on contaminated work surfaces, drug vials and containers, contaminated clothing and medical equipment, and in patient excreta and secretions such as urine, feces, and sweat. The toxicity of antineoplastic drugs is well recognized and includes acute effects such as nausea and vomiting, blood count declines and skin and mucous membrane irritation. Also well recognized in treated patients are these drugs' reproductive and developmental toxicity[1].

Routine work activities can result in spills, create aerosols or generate dust, thereby increasing the potential of exposure[1–4]. Skin absorption and inhalation are the most common ways a healthcare worker is exposed to antineoplastic drugs. However, ingestion (from hand-to-mouth contact), accidental injection through a needle stick, or other sharps injury is also possible[5]. These workplace exposures to antineoplastic drugs have been associated with health effects such as skin disorders, adverse reproductive outcomes, and certain cancers[1,6–9]. Workers with potential exposure include pharmacy and nursing personnel, physicians, physicians' assistants, nurse practitioners, operating room personnel, shipping and receiving personnel, waste handlers, maintenance and housekeeping workers, laundry workers, laboratory personnel, and workers in veterinary practices and others working in healthcare settings who come into contact with drugs or drug waste[1].

Occupational exposure characteristics

Numerous published reports have documented: (1) Workplace contamination with a small percentage of the total number of antineoplastic drugs currently in use (presumably similar for others, but not known at this time); (2) Uptake of antineoplastic drugs as indicated by measurable amounts of the drugs in the urine of healthcare workers; and (3) Significant increases in biomarkers of genotoxicity in healthcare workers compared to control populations[10]. At the present time, measurement of surface contamination is the best indicator of the level of environmental contamination in areas where antineoplastic drugs are prepared, administered to patients, or otherwise handled (such as receiving areas, transit routes throughout the facility, and waste storage areas)[11]. Based on over 100 published studies, the majority of work-places where antineoplastic drugs are handled are contaminated with antineoplastic drugs and numerous studies have demonstrated worker exposure to these drugs[10,12]. Some studies have shown an association between surface contamination and worker exposure[13–15]. Industrial hygiene studies suggest that work-place contamination with antineoplastic drugs in the United States has not changed considerably over the past decade or more, indicating that worker exposure probably has not changed considerably, despite efforts to reduce or eliminate environmental contamination[14,16–19].

The introduction of Class II biological safety cabinets (BSCs) for the preparation of antineoplastic drugs in the 1980s substantially reduced the potential for worker exposure[20], but not as efficiently as first believed[16]. More recent attempts to reduce or eliminate workplace contamination have included using engineering controls such as compounding aseptic containment isolators (CACIs), robotic systems, and closed system drug transfer devices (CSTDs)[17–19, 21–23]. This research suggests that even when these controls are used in healthcare settings, the potential for exposure to antineoplastic drugs cannot be completely eliminated[12,14, 18,19,24–31].

Antineoplastic drugs listing and contraindications during pregnancy

In 2004, NIOSH published an "Alert" document on antineoplastic and other hazardous drugs that described safe handling practices for all healthcare workers[1]. The alert also included a list of drugs that were considered hazardous to workers based on the hazardous drug definition that includes properties of mutagenicity, carcinogenicity and reproductive or developmental toxicity. That list of hazardous drugs was most recently updated in 2014 and approximately one-half of drugs listed as hazardous by NIOSH are classified as antineoplastic while the remainder comprise hormonal agents, immunosuppressants, antiviral agents, and others[5].

Of the 184 drugs identified as hazardous by NIOSH, 99 possess precautionary labeling from the FDA as Pregnancy Category D and 43 are listed as Pregnancy Category X, indicating the potential for fetal harm. The remainder of the listed drugs are Category C or B. Pregnancy Category A is characterized as adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy; Pregnancy Category B is characterized as animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, and Pregnancy Category C is characterized as animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. For Category D drugs, there is positive evidence of human fetal risk, based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks to the fetus. Category X drugs are those for which the fetal risk clearly outweighs the benefits to patients[31–33].

Although published reports of adverse reproductive outcomes among healthcare workers pertain to exposure to antineoplastic drugs, the studies may be generalized to include healthcare workers exposed to other hazardous drugs. NIOSH has identified hazardous drugs that are used to treat noncancerous conditions[5]. Many of these drugs are reproductive hazards and are classified as FDA Pregnancy Category D or X. Some examples of hazardous drugs other than antineoplastic drugs that produce adverse reproductive effects in patients treated with them include: thalidomide, diethylstilbestrol, valproic acid and products containing valproic acid, paxil, ribavirin, and finasteride[34–41].

According to the FDA, the current pregnancy category labeling may be misleading[42]. Using A, B, C, D and X to describe the risk of fetal harm implies that risk increases from one category to the next. In fact, C- and D-category drugs may have risks similar to those in category X, but risk is weighed against benefit. When considered in the context of occupational exposure, there are no benefits associated with drug exposure; therefore, occupational exposure of pregnant workers cannot be assumed to be harmless.

Biologic mechanisms

A substantial number of the drugs have been identified by NIOSH as hazardous and are also suspected or known human carcinogens[5,43]. Many are teratogenic and have adverse reproductive effects. The severity of the teratogenic effects depends on the drug, the dose, and the developmental stage of the fetus at exposure. Schardein[44] lists several common antineoplastic drugs as human teratogens. Although information is available from human studies about individual drug exposures, most malignancies are treated with multi-drug regimens. Therefore, many of the known teratogenic effects of individual drugs have been derived from animal studies. The literature on adverse reproductive effects of antineoplastic drugs in laboratory studies is beyond the scope of this publication. Drug package inserts for the antineoplastic drugs list adverse reproductive effects, including lethality, in animal studies at, and often below, the recommended human dose[45]. Reproductive health is one of the most vulnerable biological events at risk from exposure to antineoplastic drugs. Moreover, it has been hypothesized that many antineoplastic drugs actually target the developing fetus in the same way they target rapidly proliferating cancer cells[46]. The risk can be influenced by the timing of exposure during discrete stages of development as well as the potency and toxicity of the hazardous drug.

Reproductive hazards can affect the reproductive function of women or men or the ability of couples to conceive or bear healthy children[47]. In women treated with antineoplastic drugs, adverse effects have been reported including damage to ovarian follicles, decreased ovarian volume, and ovarian fibrosis resulting in amenorrhea and menopausal symptoms[48]. For pregnant women, the “window of risk” begins approximately one month before conception and lasts through the pregnancy, though data from treated patients indicates the most vulnerable window of risk occurs in the first trimester. In addition, numerous hazardous drugs are known to enter the breast milk of treated patients[32,47,49,50]; therefore, the infants of healthcare workers have the potential to be exposed during breastfeeding if exposure to the mother occurs. In men, reported adverse effects include primary or secondary hormonal changes. In addition, a man can expose his female partner and/or her developing fetus via contaminants on his skin or clothing, or during sexual intercourse[51]. Men produce sperm over approximately a 2-month cycle; therefore, a man’s sperm is vulnerable to hazardous exposures from as early as 2 months before conception[52]. Infertility following treatment with antineoplastic drugs has been reported for both men and women because of the gonadal toxicity of the drugs[53–55]. Consequently, both male and female workers who are handling antineoplastic drugs during any of these critical reproductive periods should be especially aware of potential risks to the health of their offspring even if their exposure is much lower than treated patients.

Although adults can be adversely affected by prolonged exposures to certain chemicals, the developing fetus and newborns up to the age of six months are usually more sensitive to chemical toxicity because of the incomplete development of systems for biotransformation and elimination. Unlike older children and adults, these pathways are underdeveloped and may be less efficient at detoxifying and excreting drugs. Therefore, in young children, toxicants may be present in higher concentrations in the blood for longer periods than would be true in older children whose detoxification and excretion pathways are more effective[56]. For many chemical exposures, it is known that the fetus is more susceptible than the mother to the toxic chemical[56–60]. In addition, studies have shown that exposure to chemicals and radiation in utero and early in life can disproportionally increase the occurrence of childhood cancer compared with exposures that occur later in life[60].

Laboratory studies have demonstrated that many antineoplastic drugs are teratogenic, often in more than one animal species. Some classes of drugs are more hazardous than others[44,61]. As a group, the antineoplastic drugs have been shown in animal studies to be some of the most potent teratogenic agents known even at doses typically used in cancer treatment. Alkylating agents, anthracycline antineoplastic antibiotics, and antimetabolites all have potent teratogenic activity in multiple animal species[44]. For the developing fetus, it is known that the placenta is not an effective barrier to low-molecular-weight molecules and it is also more permeable to lipophilic chemicals and drugs. In patients treated with drugs, many antineoplastic and other hazardous drugs can reach the fetus in concentrations that could have deleterious effects[62].

In the United States, there are an estimated 8 million healthcare workers potentially exposed to hazardous drugs[63]; it is not known how many of them actually have exposure to antineoplastic drugs. However, the majority of these healthcare workers are women of reproductive age who are at increased risk for adverse reproductive outcomes[64,65]. The actual number of men and women who may be at reproductive risk while exposed to hazardous drugs, although less than 8 million, is still quite large.

Therapeutic exposure to antineoplastic drug and reproductive effects

There is a wealth of information documenting the adverse reproductive effects of antineoplastic drugs in patients who have been treated with them. Four recent publications have reviewed and summarized the effects of cancer treatment on the developing fetus[46, 66–68]. Although data are limited or not available for many drugs, the authors concluded that, in general, antineoplastic drugs have their principal adverse effects on the fetus during the first trimester. Therapeutic exposure during the first 2–3 weeks of pregnancy typically results in miscarriage but not teratogenesis. Brief treatment-related exposures during early pregnancy to antineoplastic drugs (those for which there are data) had little effect on the fetus. However, continued exposure resulted in congenital anomaly rates of approximately 20%. Findings about single-agent exposures were mixed; perhaps due to small sample sizes, but Selig[46] noted that exposure of the fetus during the first trimester was most critical, though effects have been seen in second and third trimester exposure[68]. Some commonly used drugs such as methotrexate, daunorubicin, and idarubicin are contraindicated during the entire pregnancy. A recent report by the National Toxicology Program[68] provides a comprehensive summary of the effects of some antineoplastic drugs on reproductive outcomes in patients. Among other outcomes, NTP reported: (1) a higher rate of major malformations following exposure during the first trimester compared to exposure in the second and/or third trimester; (2) an increase in the rate of stillbirth following exposure in the second and/ or third trimester; and (3); abnormally low levels of amniotic fluid (primarily attributable to trastuzumab). This report also briefly addresses occupational exposure to these drugs and possible adverse reproductive outcomes in healthcare workers.

Methods

An extensive review of the literature linking occupational exposure to antineoplastic drugs and adverse reproductive effects was conducted in February 2014 using the following databases: Canadiana, CI-NAHL, CISILO, DTIC, Embase, Health & Safety Science Abstracts, HSELine, NIOSHTIC-2, NTIS, OSHLine, PubMed, Risk Abstracts, Toxicology Abstracts, Toxline, Web of Science and WorldCat searching from 1980 to February 2014. Using the MeSH controlled vocabulary the following search was performed in PubMed: (“Antineoplastic agents/adverse effects”[Mesh] OR “antineoplastic agents/prevention and control”[Mesh] OR “Cytotoxins”[Mesh] OR “Hazardous Substances/adverse effects”[Mesh] OR “Hazardous Substances/toxicity”[Mesh] OR “Pharmaceutical Preparations/adverse effects”[Mesh] OR antineoplastic[TI] OR cytotoxic[TI] OR cytostatic[TI] OR chemotherap*[TI]) AND (“Personnel, Hospital”[Mesh] OR “Health Personnel”[Mesh]) AND (“Occupational Exposure”[Mesh:NoExp] OR “Occupational Diseases”[Mesh] OR “Environmental Exposure”[Mesh] OR occupational[TI]) AND (“Reproduction”[Mesh] OR “Infertility”[Mesh] OR “Fertility”[Mesh] OR “Pregnancy Complications”[Mesh] OR pregnan*[TI] OR infertility[TI] OR reproducti*[TI]). The other databases were searched using the following key word search strings: (antineoplastic OR chemotherapeutic OR cytotoxic OR cytostatic) AND (pregnan* OR infertility OR reproducti*) AND occupational.

The initial electronic database search was supplemented by manual searches of published reference lists, review articles and conference abstracts.

All English language, peer-reviewed publications that were obtained were included in this document. Meeting abstracts were not included. Overall, 18 individual studies were reviewed, some with multiple endpoints.

Results

Table 1 summarizes studies of occupational exposure to antineoplastic drugs and congenital anomalies in offspring, including eight studies. The primary limitation of these studies is the small sample sizes; five of the eight studies had 10 or fewer exposed cases, and all studies had fewer than 20 exposed cases. The small sample sizes resulted in several other important limitations. These included a limited ability to adjust for confounding; the need to group anomalies that had different etiologies; and wide confidence intervals, which reflect poor statistical power. However, of the studies that had more than five exposed cases, three showed significantly increased risks associated with exposure [69–71], and two showed increased risks that were not statistically significant[7,9]. The odds ratios of adjusted models ranged from 1.36 (95% confidence interval, 0.59–3.14)[7] to 5.1 (95% confidence interval, 1.1–23.6)[71]. A meta-analysis[72] of four studies with exposure periods ranging from 1966 to 1985[7,69,71,73] reported a crude odds ratio of 1.64 (95% confidence interval, 0.91–2.94) for all congenital anomalies combined. Although these previous studies suggest an increased risk for congenital anomalies with maternal occupational exposure, the limitations and wide confidence intervals make the size of the adverse effect uncertain. In addition, studies are needed that reflect current exposure levels as the studies published to date include data that was collected prior to the year 2000.

Studies of maternal occupational exposure to antineoplastic drugs and miscarriage are shown in Table 2. We identified eight studies evaluating miscarriage, an additional three studies that analyzed combined outcomes of miscarriage and stillbirth, four studies of stillbirths, and two studies of tubal pregnancies. The studies of miscarriage had mixed results, and three of these studies were limited by small sample sizes (fewer than 20 exposed cases). The three largest studies[74–76] showed increased occurrence of miscarriages among women who reported handling of antineoplastic drugs during the first trimester. Most exposures were among oncology nurses or pharmacists. Other studies that did not find statistically significant associations had odds ratios ranging from 0.7 to 2.8. A meta-analysis[22] that pooled the results of five studies[7,71,74,75,77] found an overall adjusted increased risk of 46% among exposed workers (95% confidence interval, 11% to 92%)[72]. All studies published to date contain data collected prior to 2002.

More research is needed to examine the effects of occupational exposure to antineoplastic drugs and stillbirth because this is an uncommon outcome and therefore difficult to study. All of the studies of stillbirths (or of fetal loss which combined miscarriage and stillbirth) had insufficient numbers of exposed cases (n = 1 to 13), resulting in wide confidence intervals [9,70,71,73,75,78,79]. We found only two studies of tubal pregnancies, both with ten or fewer exposed cases, and the results varied widely from OR=0.95 (95% CI 0.39–2.31)[80] to OR 11.4 (95% CI 2.7–17.6)[81].

We found only two studies of occupational exposure to antineoplastic drugs and fertility and time to pregnancy (Table 3), though the results suggest that exposure to antineoplastic drugs is associated with an increased risk of subfertility[79,82]. Only one study evaluated menstrual cycle characteristics; it showed a statistically significant three-fold increased risk of menstrual cycle irregularities from occupational exposure to antineoplastic drugs[83]. A study of Danish oncology nurses showed no statistically significant differences in birth weight, gestational age, or sex ratio among exposed mothers[7], while a study of French oncology nurses exposed to antineoplastic drugs found the mean birth weight of offspring to be lower than that the unexposed[84].

Discussion

Although there is some variability in the size of the adverse outcomes observed among occupational cohorts reviewed here, the findings are generally indicative of an increased risk of adverse reproductive outcomes with occupational exposure, especially with exposures during the first trimester of pregnancy. While all of the studies published to date were conducted before the release of the NIOSH Alert in 2004, environmental exposure studies since 2004 have documented that workplaces are still commonly contaminated with these drugs[12,14,18,19,24–30] and hence, workers are likely chronically exposed to low levels of multiple agents known to be toxic to human reproduction. A workplace should be safe for all workers, regardless of their reproductive status and this includes workplaces where antineoplastic drugs are used[85]. When the reproductive outcomes data reviewed here are considered in light of their biologic plausibility based on mechanisms of drug action and for their consistency with the results of animal and patient studies, a coherent body of evidence emerges. This evidence suggests the need for specific guidance for healthcare workers exposed to antineoplastic and other hazardous drugs, which assures protections for their reproductive health and the well-being of their offspring.

Given the unique vulnerability to exposure of the developing fetus and a newborn infant described above, and also given the potentially devastating impact of such exposures, several professional and government organizations have recommendations in place for alternative duty or temporary reassignment for healthcare workers who may be at risk of exposure to hazardous drugs during critical, vulnerable periods in reproduction[3,4,47,86–91]. Typically, these vulnerable windows include times when couples (males and females) are actively trying to conceive and when women are pregnant or breast-feeding. Since 1995, OSHA has recommended that healthcare facilities have a policy in place regarding reproductive risks associated with occupational exposure of workers to hazardous drugs and that such a policy should be followed[2]. Britain's Health and Safety Executive and other professional bodies recommend that an initial risk assessment should be performed in order to determine if there is potential reproductive harm to the fetus or offspring[47,92]. However, because there are no established permissible exposure limits (PELs) or other guidance values for these drugs[1], a classical risk assessment is often not possible. Therefore, other exposure assessments may be applied here. Although a precise dose of a hazardous drug may not be estimated for a given work task, the likelihood of some exposure can be assumed given the environmental contamination data described above. Beyond the benefits to the health of workers and their offspring, providing accommodations to expectant and nursing workers makes good business sense since it is estimated that 68% of working women will become pregnant at least once during their working life[93]; moreover, according to the U.S. Census Bureau, two-thirds of women work during their first pregnancy, and more than half (55%) of all births are to working women[94]. Family friendly workplace policies reduce turnover, and increase morale and productivity. Because of the possibility that healthcare workers may be exposed to low levels of many drugs with adverse reproductive effects, additional vigilance and protections might be required for those healthcare workers who are most vulnerable to the reproductive and developmental effects of hazardous drugs[2,3,4,47,87,90,95].

The primary limitation of the studies we evaluated is the era of the data collection; all studies published to date evaluate data collected prior to 2002, and most data were collected in the 1980's. Though there has been a lot of attention recently to raise awareness of controlling exposures, studies continue to show that exposures are still occurring. Another important limitation of the literature is the small sample sizes, particularly the small numbers of exposed cases. Because of this limitation, studies were often unable to adjust for confounding factors and reported wide confidence intervals. However, most of the studies we reviewed that had larger relative sample sizes indicated an increased risk of adverse reproductive health outcomes. Though there are few studies of fertility, there appears to be an indication of a risk with exposure. A data gap we identified is a lack of data on later childhood health of offspring exposed in utero. One study that was published as a dissertation showed an increased risk of learning disabilities among offspring of workers exposed to antineoplastic drugs[96]. Finally, most studies lacked enough statistical power or proper exposure assessment to evaluate dose. Thus, until more current studies are available on occupational exposures, we recommend reducing or avoiding exposures until better epidemiologic data show the risk is no longer occurring.

Considering the biologic plausibility of the mechanisms of action of many hazardous antineoplastic drugs, and observations of adverse reproductive and developmental health outcomes observed in treated cancer patients, this review suggests, fairly consistently that, there are also elevated risks to reproductive health for exposed workers. Workplace contamination studies indicate that hazardous drug exposure is widespread, commonly occurring during any handling activity, despite use of current safety guidance. Therefore, additional precautions to prevent exposure during uniquely vulnerable windows of fetal and newborn development should be considered.

Acknowledgments

We would like to thank Kathleen Connick for assistance with the database searches and Patricia Mathias for assistance with the citations. We would like to acknowledge Andrew S. Rowland, Linda A. McCauley, and Elizabeth A. Whalen for their critical review of this manuscript.

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Table 1

Studies of Congenital Anomalies Associated with Occupational Exposure to Antineoplastic Drugs

Reference	Exposure Period	Study Location	Population	Study Design	Overall Sample Size	Number of exposed cases	Results	Comments
Fransman et al. 2007	1990–1997	Netherlands	Oncology & other types of nurses	Survey	1,519	5 in highest exposure category	No significant associations; CIs were wide	Retrospective exposure assessment was based on frequency of tasks; estimated dermal exposure. No evidence of dose response.
Hemminki et al. 1985	<1985	Finland	Finnish hospital nurses	Case–control; survey	38 cases; 99 controls	19	Adj OR, 4.7 (1.2–18.1)	11 exposed cases handled less than 1/week; 8 expo cases handled once or more per week.
McAbee et al. 1993	1985	US	Nurses and university employees	Cross- sectional survey	633 women (1,133 pregnancies)	10	Oncology nurses reported more birth defects than the control group (p = 0.02 for crude analysis).	Response rate was 30%; analyzed first pregnancies separately from each additional pregnancy
McDonald et al. 1988	1982–1984	Montreal	Population based; doctors and nurses	Survey	152 exposed pregnancies	8	8/4 = observed / expected	Used medical records
Peelen et al. 1999	<1985	Netherlands	Oncology nurses	Survey	229 exposed + 956 unexposed	7	OR, 5.1 (1.1–23.6) among nurses who prepare hazardous drugs	Had to work in oncology for 2 months or more during pregnancy
Ratner et al. 2010	1974–2000	Canada	RNs	Survey; registry	12,741	17	Adj OR, 1.42 (0.86–2.36)	Based on RNs who were ever or never employed in oncology
Skov et al. 1992	1985	Denmark	Oncology nurses	Retrospective cohort	266 exposed +770 unexposed	16	Adj OR, 1.36 (0.59–3.14) in highest exposure category	Prepared or administered hazardous drugs during pregnancy
Lorente et al. 2000	1989–1992	Europe	Population- based	Case–control	64 cleft lip / palate + 36 cleft palate + 751 controls	3	Cleft lip: OR, 3.35 (0.37–3.12); Cleft palate: OR, 11.25 (1.98–63.7)	Note the wide CIs.

Table 2

Studies of Miscarriage, Stillbirth, Tubal Pregnancy Associated with Occupational Exposure to Antineoplastic Drugs

Reference	Exposure Period	Study Location	Population	Study Design	Overall Sample Size	Number of exposed cases	Results	Comments
Fransman et al. 2007	1990–1997	Netherlands	Oncology and other types of nurses	Survey	1,519	34, but divided into 3 categories	No significant associations; CIs were wide for miscarriage	Too many categories for small numbers; sample sizes were not clearly reported. Retrospective exposure assessment among nurses
Hemminki et al. 1985	<1985	Finland	Finnish hospital nurses	Case-control	169 cases + 469 controls	12	Adj OR, 0.8 (0.3–1.7) for miscarriage	50% Response rate
Lawson et al. 2011	1993–2001	U.S.	U.S. nurses	Survey	775 cases + 6,707 live births	48	Adj OR, 1.94 (1.32–2.86) for miscarriage	
Peelen et al. 1999	<1985	Netherlands	Oncology nurses	Survey	249 exposed + 1,010 unexposed	Unclear	OR, 1.4 (0.8–2.6) for miscarriage	Small numbers, limitations in study design. See Fransman study that replaces this study.
Selevan et al. 1985	<1985	Finland	Nurses	Case–control	124 cases +321 controls	18	OR, 2.3 (1.21–4.39) for miscarriage	First-trimester exposure to hazardous drugs more than once per week
Skov et al. 1992	1985	Denmark	Oncology nurses	Retrospective cohort	281 exposed + 809 unexposed	18	Adj OR, 0.74 (0.40–1.38) for miscarriage	Prepared or administered hazardous drugs anytime during pregnancy
Stücker et al. 1990	1985	France	Hospital personnel	Survey	139 exposed +357 unexposed	36	Adj OR, 1.7 (1.03–2.80) for miscarriage	Prepared hazardous drugs
Valanis et al. 1999	1985	U.S.	Nurses and pharmacists	Survey	1,448 exposed + 5,297 unexposed	223	Adj OR, 1.50 (1.25–1.80) for miscarriage	Exposure to hazardous drugs during pregnancy
McDonald et al. 1988	1982–1984	Montreal	Population based	In-person survey	22,613	13	13 observed / 13.4 expected miscarriages and stillbirths	Administered hazardous drugs during 1st trimester
McAbee et al. 1993	1985	U.S.	Nurses and university employees	Cross- sectional survey	663 women (1,133 pregnancies)	3	Adj OR of 0.67 for	Low response rates (<30%)

Reference	Exposure Period	Study Location	Population	Study Design	Overall Sample Size	Number of exposed cases	Results	Comments
							miscarriage and stillbirth miscarriage and stillbirth	
Rogers and Emmett 1987	<1985	U.S.	Oncology and community health nurses	Survey	233	13	OR, 2.5 ($p <$ 0.04) for miscarriage and stillbirth	OR didn't change with adjustment for age
Fransman et al. 2007	1990–1997	Netherlands	Oncology & other types of nurses	Survey	1,519	1 in the highest category	No significant associations; CIs were wide for stillbirth	Retrospective exposure assessment of frequency of tasks, dermal exposure
Peelen et al. 1999	1990–1997	Netherlands	Oncology nurses	Survey	249 exposed + 1,010 unexposed	2	OR, 1.2 (0.65–2.20) for still-birth	Small numbers
Valanis et al. 1999	1985	U.S.	Nurses and pharmacists	Survey	7,094	12	Adj OR, 1.10 (0.55–2.20) for stillbirth	
Ratner et al. 2010	1974–2000	Canada	RNs	Cohort	147/23,222	3	Adj OR, 0.67 (0.21–2.13) for stillbirth	
Bouyer et al. 1998	1993–1994	France	Hospital personnel	Case–control	104 cases/ 279 controls	10	Adj OR, 0.95 (0.39–2.31) for tubal pregnancy	Studied only preconception exposures. Update of Saurel- Cubizolles 1993 article. Could have over-adjusted; included previous SA in analysis. CIs were wide, so power is a question.
Saurel-Cubizolles et al. 1993	1985	Paris	Hospital nurses	Self- administered survey	85 exposed and 599 unexposed	6	Adj OR, 11.4 (2.7–17.6) for tubal pregnancy	Exposure to hazardous drugs during 1st trimester. See Bouyer update from 1998.

Table 3

Studies of Fertility, Time to Pregnancy, Menstrual Function, Birthweight, Gestational Age, Sex Ratio, and Learning Cognitive Function in Offspring Associated with Occupational Exposure to Antineoplastic Drugs

Reference	Exposure Period	Study Location	Population	Study Design	Overall Sample Size	Number of exposed cases	Results	Comments
Valanis et al. 1997	<1985	U.S.	Nurses and pharmacy personnel	Case- control	405 cases+ 1,215 controls	78	OR, 1.5 (1.1– 2.0) for infertility	
Fransman et al. 2007	1990–1997	Netherlands	Oncology and other types of nurses	Survey	126	26 in highest category	Hazard ratio, 0.8 (0.6–−0.9) for time to pregnancy	Retrospective exposure assessment among nurses
Shortridge et al. 1995	1986	U.S.	ONS and ANA members	Survey	1,458	172	Adj OR, 3.4 (1.6–7.3) for menstrual dysfunction among nurses who administer chemotherapy	Menstrual dysfunction defined as one of the following: a) 3+ months of no periods, b) cycle length of <25 or >31 days, or c) flow duration of <2 or >7 days
Skov et al. 1992	1985	Denmark	Oncology nurses	Retrospective cohort	266 exposed / 770 unexposed	266	No statistically significant differences in adjusted analyses between exposed and unexposed for birthweight, gestational age, or sex ratio	
Stücker et al. 1993	1985–1986	France	Oncology nurses	Survey	420 Singleton live births	107 exposed pregnancies	In adjusted models, mean birthweight of exposed pregnancies was 56 g lower than unexposed (95% CI, minus 155.1 to 43.1)	No difference in gestational age between exposed and unexposed

Abbreviations used: OR-odds ratio; AdOR-adjusted odds ratio; CI-confidence interval